production, likely due to reduced competition between matrix consumption and the exogenous detection system and, iii) alters the steady state extramitochondrial H_2O_2 concentration maintained by energized mitochondria. Taken together, our results are consistent with the notion that, at least under some conditions, mitochondria are not a major source of ROS in the form of H_2O_2 in muscle cells and instead they may play an integral component of the cellular antioxidant system.

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Mitochondria-targeted antioxidants prevent TNFα induced endothelial cell damage

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Using mitochondria-targeted antioxidants made of plastoquinone and penetrating cations (SkQ family), we investigated the role of mitochondrial reactive oxygen species (ROS) in the TNFα-induced cytoskeleton reorganization and apoptosis in endothelial cells. SkQ (0.2–20 nM), as well as the classic antioxidant N-acetylcysteine (5 mM) and Trolox (200 μM) significantly suppressed apoptosis induced by TNFα [1]. Their action was directed at suppressing the release of cytochrome c. We showed that SkQ treatment led to an increased level of Bcl-2, and reduced levels of Bax and p53 [1]. Nevertheless, SkQ had no Bcl-2 mRNA expression, but it enhances Bcl2 phosphorylation thus contributing to the inhibition of protein ubiquitination. We have also shown that SkQ prevents Bcl-2 proteolysis induced by TNFα. We assume that SkQ may affect activation of the redox sensitive stress kinases that are involved in the phosphorylation of the Bcl-2 family proteins. We showed that SkQ inhibited TNFα-induced monolayer endothelial permeability for dextran (65–85 kDa MW). Endothelial monolayer permeability induced by TNFα is accompanied by cytoskeleton reorganization. SkQ prevented TNFα-induced release of VE-cadherin and β-catenin from the contact area, as well as disassembly of circular peripheral actin microfilament. TNFα-activated matrix metalloproteinases (MMP) cleaved extracellular fragment of VE-cadherins. We observed MMP-dependent decrease in the overall VE-cadherin level in the cells and the appearance of its cleavage product in the cell medium induced by TNFα. These effects were markedly suppressed by SkQ. Thus, it was shown that TNFα-dependent endothelial cell damage was largely dependent on ROS production in mitochondria, thus indicating promising angioprotective action of SkQ.

Reference

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